REMARKS

Claim amendments

Claims 5 and 9 have been canceled.

Claims 1 and 6 have been amended to more clearly indicate that the molecule is not HIF and the molecule is selected from the group consisting of: 5β pregnane-3,20-dione, 5β-pregnane 3- β-ol-20-one, 3α-hydroxy-5α-pregnane-20-one, prenane-3 β,5 β-diol 20-one, 3β hydroxy 5α-pregnane-20-one, 5β-reductase, 3β-hydroxysteroid oxidoreductase, 5β-hydroxylase, 5α-reductase, 3α-hydroxysteroid dehydrogenase/oxydoreductase and a combination thereof. Support for the amendment can be found, for example, on page 10, line 19 – page 12, line 8; and Figure 1 of the specification.

Claim 10 has been amended to correct a typographical error.

Claims 12, 16, 19, 21 and 23 have been amended to replace "ÿ-3-ÿ" with "Δ5-3-β". Support for the amendment can be found, for example in original Claims 12, 16, 19, 21 and 23 of the specification.

No new matter has been added.

Claim Objections

Claims 5 and 9 are objected to because "Δ5-3-β" in the original claims has been changed to "ÿ-3-ÿ" in the claims filed November 24, 2006.

Claims 5 and 9 have been canceled, thereby obviating the objection.

Rejection of Claims 1, 2, 4, 6, 7 and 8 under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4, 6, 7 and 8 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the written description requirement" (Office Action, first page 3). The Examiner states that "[w]hile the specification discloses specific molecules which are involved in the biosynthetic pathway for HIF, the claims encompass use of known molecules which are not disclosed in the specification or prior art as associated with the biosynthetic pathway for HIF" and "molecules not necessarily known in the prior art or disclosed in the specification such as

novel enzymes involved in steroid biosynthesis" (Office Action, second page 2). The Examiner further states that "[w]ith the exception of aforementioned molecules disclosed in the specification, the skilled artisan cannot envision the detailed structure of the encompassed molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation" (Office Action, second page 2).

Applicants respectfully disagree. Nevertheless, in order to further prosecution, the claims have been amended to recite the specific molecules which are involved in the biosynthetic pathway for HIF as disclosed in the specification. That is, the claims have been amended to indicate that the molecule is not HIF and the molecule is selected from the group consisting of: 5β pregnane-3,20-dione, 5β-pregnane 3- β-ol-20-one, 3α-hydroxy-5α-pregnane-20-one, prenane-3 β,5 β-diol 20-one, 3β hydroxy 5α-pregnane-20-one, 5β-reductase, 3β-hydroxysteroid oxidoreductase, 5β-hydroxylase, 5α-reductase, 3α-hydroxysteroid dehydrogenase/oxydoreductase and a combination thereof.

Applicants have provided written description for the claimed invention, particularly as amended.

Rejection of Claims 1, 2 and 4-9 under 35 U.S.C. §103(a)

Claims 1, 2 and 4-9 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Parhami-Seren et al. (WO 01/25281) in view of Hughes et al. (WO 01/03687), Lu et al. and Nussdorfer et al." (Office Action, pages 4-5). The Examiner cites Parhami-Seren *et al.* as teaching that "antibodies against the steroid OLC (aka HIF . . .) can be used to treat hypertension"; that the "method would have been used to treat any form of hypertension involving OLC such as essential hypertension" and "methods for making and identifying such antibodies" (Office Action, page 5). The Examiner cites Hughes *et al.* as teaching "an inhibitor of enzymatic activity involved in the biosynthesis of a steroid molecule can be used to prevent synthesis of said molecule and therefore treat a disease mediated by said molecule"; Lu *et al.* as disclosing that "EO (aka OLC/HIF) is a steroid molecule that is formed from pregnenolone/progesterone"; and Nussdorfer *et al.* as disclosing that the "enzymes recited in

claim 5/9 are involved in the synthesis of pregnenolone/progesterone" (Office Action, page 5). It is the Examiner's opinion that

> "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Parhami-Seren et al. teach that antibodies against the steroid OLC (aka HIF) can be used to treat hypertension and methods for making and identifying such antibodies whilst Hughes et al. discloses that an inhibitor of enzymatic activity involved in the biosynthesis of a steroid can be used to prevent synthesis of said molecule and therefore treat a disease mediated by said molecule, Lu et al. disclose that EO (aka OLC/HIF) is a steroid molecule that is formed from pregnenolone/progesterone and the prior art recognized that the enzymes recited in claim 5/9 are involved in the synthesis of pregnenolone/progesterone (Figure 3). One of ordinary skill in the art would have been motivated to do the aforementioned because Hughes et al. discloses that an inhibitor of enzymatic activity involved in the biosynthesis of a steroid molecule can be used to prevent synthesis of said molecule and therefore treat a disease mediated by said molecule, inhibitory antibodies were known in the art as per Parhami-Seren et al. and it would have been necessary to screen for such antibodies to identify them (Office Action, pages 5-6).

Applicants respectfully disagree. Applicants' invention is based on the discovery of the HIF biosynthetic pathway and identification of candidate genes encoding enzymes in the pathway. As noted above, the claims have been amended to more clearly recite a method of identifying an agent that alters the activity of HIF, comprising contacting a molecule in a biosynthetic pathway for HIF with an agent to be assessed *wherein the molecule is not HIF and the molecule is selected from the group consisting of: 5β pregnane-3,20-dione, 5β-pregnane 3-β-ol-20-one, 3α-hydroxy-5α-pregnane-20-one, prenane-3 β,5 β-diol 20-one, 3β hydroxy 5α-pregnane-20-one, 5β-reductase, 3β-hydroxysteroid oxidoreductase, 5β-hydroxylase, 5α-reductase, 3α-hydroxysteroid dehydrogenase/oxydoreductase and a combination thereof*; and determining the activity of the molecule in the presence of the agent.

Parhami-Seren *et al.* teach "a monoclonal antibody (mAb) or antigen binding fragment thereof having binding specificity for ouabain, wherein the antibody or antigen binding fragment does not cross react with digoxin" and use of the antibody of binding fragment thereof for diagnosis and therapy (Parhami-Seren *et al.*, page 7, lines 18-20). As the Examiner notes,

Parhami-Seren *et al.* "do not teach the claimed method wherein the antibody identified and used would be against a molecule in the HIF biosynthetic pathway" (Office Action, page 5). Parhami-Seren *et al.* do not teach or even suggest a biosynthetic pathway for the generation of HIF. Furthermore, as noted above, the claims have been amended to more clearly indicate that the agent is contacted with a molecule in the HIF biosynthetic pathway wherein the molecule is not HIF.

Hughes *et al.* teach "combined use of phytosterol and phytoestrogen compounds in a method of inhibiting biosynthesis or bioactivity of an endogenous steroid sex hormone in a human subject" which involves "administering to a human subject a combination of a dose of at least one phytosterol compound together with a dose of at least one phytoestrogen compound in an amount sufficient to inhibit biosynthesis or bioactivity of an endogenous steroid sex hormone" (Hughes *et al.*, page 8, lines 10-15). There is no mention in the Hughes *et al.* reference of HIF.

Lu *et al.* teach that "pregnenolone and progesterone are intermediates in the adrenal biosynthesis of EO [endogenous ouabain-like steroid]" (Lu *et al.*, P131). As noted in Figure 1 of the subject application, the generation of pregnenolone and progesterone appear very early in the HIF biosynthetic pathway. Lu *et al.* provide no further teaching or suggestion of any subsequent steps in the HIF biosynthetic pathway.

Nussdorfer *et al.* summarize "the current knowledge of the molecular and cell biology of ETs [endothelins] and steroid-secreting tissues" and discuss "findings indicating that locally synthesized ETs are involved in the autocrine/paracrine control of secretion and growth of steroid-secreting tissues" (Nussdorfer *et al.*, page 406, column 2). Figure 3 in the Nussdorfer *et al.* reference is a "[p]athway of hormone synthesis and degradation in steroid-secreting cells" showing the steps of conversion of cholesterol to pregnenolone by P450scc, and transformation of pregnenolone into progesterone by 3β-HSD (Nussdorfer *et al.*, Figure 3). However, Nussdorfer *et al.* provide no further teaching or suggestion of any subsequent steps in the hormone synthesis pathway that overlap with the specific biosynthetic pathway of HIF.

Combination of Parhami-Seren et al., Hughes et al., Lu et al. and Nussdorfer et al.

Of the references cited, only Lu *et al.* specifically discuss the biosynthetic pathway of

HIF, however, Lu *et al.* only discloses intermediate molecules that are present in the early stages of HIF biosynthesis (*i.e.*, pregnenolone and progesterone). Parhami-Seren *et al.* describe antibodies directed against the end product of the HIF biosynthetic pathway, however, Parhami-Seren *et al.* do not discuss or mention the biosynthetic pathway of HIF. Clearly, a combined teaching of Parhami-Seren *et al.* and Lu *et al.* would not make obvious to one of skill in the art Applicants' HIF biosynthetic pathway "leading from cholesterol as a precursor through intermediate hydroxylation steps consistent with generation of a steroid intermediate(s), which after lactone ring addition and glycosylation results in generation of Oua, its isomer or a related derivative" (specification, page 7, lines 23-26).

The remaining references do not discuss HIF. Nussdorfer *et al.* describe a general hormone synthesis and degradation pathway for steroid-secreting cells which involves the conversion of cholesterol to pregnenolone by P450scc, and the transformation of pregnenolone into progesterone by 3β-HSD, however, no other subsequent steps in the hormone synthesis pathway overlap with the specific biosynthetic pathway of HIF. Hughes *et al.* describe the combined use of phytosterol and phytoestrogen compounds in a method of inhibiting biosynthesis or bioactivity of an endogenous steroid sex hormone. Combining the teachings of Hughes *et al.* and Nussdorfer *et al.* with the teachings of Lu *et al.* and Parhami-Seren *et al.* do not provide further insight or guidance for generation of the HIF biosynthetic pathway to one of skill in the art.

Consequently, the combined teaching of Parhami-Seren *et al.*, Hughes *et al.*, Lu *et al.* and Nussdorfer *et al.* cannot render obvious Applicants' claimed method of identifying an agent that alters the activity of HIF, comprising contacting a molecule in a biosynthetic pathway for HIF with an agent to be assessed wherein the molecule is not HIF and the molecule is selected from the group consisting of: 5β pregnane-3,20-dione, 5β-pregnane 3- β-ol-20-one, 3α-hydroxy-5α-pregnane-20-one, prenane-3 β,5 β-diol 20-one, 3β hydroxy 5α-pregnane-20-one, 5β-reductase, 3β-hydroxysteroid oxidoreductase, 5β-hydroxylase, 5α-reductase, 3α-hydroxysteroid dehydrogenase/oxydoreductase and a combination thereof; and determining the activity of the molecule in the presence of the agent.

Clearly, the combined teaching of Parhami-Seren *et al.*, Hughes *et al.*, Lu *et al.* and Nussdorfer *et al.* do not render obvious Applicants' claimed method, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J Collins

Anne J. Collins
Registration No. 40,564
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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